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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,842	11/17/2000	Roger Briesewitz	STAN-131	8224

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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/716,842	BRIESEWITZ ET AL.	
	Examin r	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- *Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.*
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-18, 22-26, 30-34 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-18,22-26,30-34 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 16-18, 22-26, 30-34 and 36 are pending.

2. In view of the amendment filed 10/2/03, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 16-18, 22-26, 30-34 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method for directing the biodistribution of a drug that binds to a protein target, wherein the drug is directed to an intracellular space upon administration to a host, said method comprising: administering to a mammalian host an effective amount of a bifunctional molecule consisting of a drug moiety and a targeting moiety to an intracellular biodistribution modulating protein optionally joined by a linking group, wherein said drug moiety binds to a protein target and said targeting moiety is selected from the group consisting of FK506, cyclosporin and rampamysin that binds to an intracellular biodistribution modulating protein to direct the biodistribution of said drug upon administration to said host to an intracellular space as compared to a free drug control, (2) the said method wherein said bifunctional molecule exhibits enhanced efficacy, (3) the said method wherein said bifunctional molecule exhibits reduced toxicity, (4) The said method wherein said bifunctional molecule consists a linking group, and (5) the said method wherein said bifunctional molecule is administered as a pharmaceutical preparation, **does not** reasonably provide enablement for a method as set forth in claims 16-18, 22-26, 30-34 and 36 wherein the drug is any undisclosed drug, any active derivative thereof, any targeting moiety that binds to any intracellular biodistribution modulating protein, any intracellular proteins, for treating *any* disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731,

737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method for directing the biodistribution of drug to a protein target to an intracellular space upon administration to a host, said method comprising: administering to a mammalian host an effective amount of a bifunctional molecule of less than about 5000 Daltons having the formula as set forth on page 6 wherein the targeting moiety of the bifunctional molecule consists of a ligand selected from the group consisting of FK506, rapamycin, and cyclosporin A that binds to intracellular protein selected from the group consisting of FKBPs. The drug moiety of the bifunctional protein is optionally joined by a linking group.

The specification does not teach how to make, much less how to use *any* method as set forth in claims 16-18, 22-26, 30-34 and 36 for the following reasons: There is insufficient guidance as to the structure of *any* "bifunctional molecule less than 5000 dalton", much less its function. The specification discloses the drug moiety of the bifunctional molecule is a small molecule that has a molecular weight of at least 50 D, but will usually not exceed about 2000 D (page 6). With regard to any drug and active derivative, the term "drug" and "active derivative thereof", there is insufficient guidance as to the structure (amino acid sequence) of said drug and "active derivative thereof, much less about its function, in turn, would be useful for directing the misdistribution of any drug that binds to any protein target for treating any disease. Further, the term "comprising" is open-ended. It expands the undisclosed drug and active derivative thereof to include additional molecule, amino acids at either or both ends. There is insufficient guidance as to the which undisclosed molecule and amino acids to be added, let alone which undisclosed protein target to which the drug binds in the claimed method. Not only the drug moiety in the bifunctional molecule is not clear in the claim, there is insufficient guidance as to the structure and binding specificity of the targeting moiety of the bifunctional molecule in the claimed method. Given the indefinite number of undisclosed targeting moiety that binds to any undisclosed biodistribution modulating protein in the intracellular space, the lack of in vivo working example in the specification,

it is unpredictable which undisclosed targeting moiety would be useful for directing the biodistribution of any drug, any active derivative thereof that binds to the undisclosed protein target for treating any disease in a mammalian host such as human.

Stryer *et al,* of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al,* of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Without the specific amino acid sequence of any drug, and active derivative thereof, and any targeting moiety, one skill in the art cannot make, much less use the claimed method.

Briesewitz *et al,* of record, teach that in general, the creation of unfavorable contacts in a bifunctional molecule that binds to intracellular protein target is far easier to achieve than favorable contacts due to steric hindrance and/or electrostatic repulsion (See page 1956, column 2, in particular). Given the indefinite number of undisclosed targeting moiety in the bifunctional molecule for the claimed method, it is unpredictable which undisclosed targeting moiety in the bifunctional molecule would be useful for the claimed method for directing the biodistribution of any drug that binds to any undisclosed protein target as a pharmaceutical preparation.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 10/2/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the FK506, rapamycin, cyclosporin A and the like... on page 21 lines 3 to 5 of the specification are representative ligands capable of serving as the z moiety (targeting moiety) and not the drug moiety. (2) Each component of the bifunctional molecule, e.g., drug moieties (page 6 to 16), targeting moiety (page 16 to21) and linking moiety (pages 22 to 23) as well as how to make these targeted bifunctional molecules (page 24 to 28) are fully described in the specification.

However, the specific biodistribution modulating protein to which the targeting moiety binds may vary greatly depending on the desired biodistribution of the bifunctional molecule and drug moiety component thereof (page 18).

The specification on page 6 defines that the drug moiety X may be any molecule as well as binding portion or fragment thereof that is capable of modulating a biological process in a living host either by itself or in the context of the biodistribution modulating protein /bifunctional molecule binary complex. The drug moiety of the bifunctional molecule may be the whole compound or a derivative thereof. e.g. its binding fragment or portion thereof that retains its affinity and activity for the target of interest. The drug moiety is capable of interacting with a target ... where such targets may be proteins, phospholipids, nucleic acids and the like where proteins are of- particular interest. Specific protein targets of interest include- without limitation enzymes, e.g. kinases- phosphatases- reductases, Cyclooxygenases proteases and the like. The specification on page 21 discloses that ligands capable of serving as the Z moiety (targeting moiety) of the bi functional include ligands the intracellular proteins. Such as: peptidyl-prolyl isomerase ligands- e.g. 17 14.506- rapamycin, cyclosporin A and the like.

It is not clear which "and the like", the derivative thereof and fragment thereof in the drug moiety as well as the targeting moiety of the bifunctional molecule is effective for the claimed method given that the specific biodistribution modulating protein to which the targeting moiety binds may vary greatly depending on the desired biodistribution of the bifunctional molecule and the undisclosed drug moiety component thereof. Further, the biodistribution modulating protein may have one or more modified residues (page 17, lines 16-20). Given the indefinite number of undisclosed targeting moiety that binds to any undisclosed biodistribution modulating protein in any mammal, the lack of in vivo working example in the specification, it is unpredictable which undisclosed targeting moiety would be useful for directing the biodistribution of any

undisclosed drug, any active derivative thereof that binds to the undisclosed protein target for treating any disease in a mammalian host such as human.

5. Claims 16-18, 22-26, 30-34 and 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of a method as set forth in claims 16-18, 22-26, 30-34 and 36 wherein the drug is any undisclosed drug, any active derivative thereof, any targeting moiety that binds to any intracellular biodistribution modulating protein, any intracellular proteins, for treating *any* disease.

The specification discloses only a method for directing the biodistribution of drug to a protein target to an intracellular space upon administration to a host, said method comprising: administering to a mammalian host an effective amount of a bifunctional molecule of less than about 5000 Daltons having the formula as set forth on page 6 wherein the targeting moiety of the bifunctional molecule consists of a ligand selected from the group consisting of FK506, rapamycin, and cyclosporin A that binds to intracellular protein selected from the group consisting of FKBPs. The drug moiety of the bifunctional protein is optionally joined by a linking group.

With the exception of the specific method of directing the biodistribution of a drug using the specific targeting moiety in the bifunctional molecule that binds to the specific intracellular protein, there is inadequate written description about the structure, much less about the function of the bifunctional molecule of less than 5000 Daltons, the bifunctional molecule consisting of any drug and active derivative thereof that binds to a protein target, and any undisclosed targeting moiety that binds to any intracellular proteins, in turn directing the drug to any intracellular space in a mammalian host such as human for the claimed method. Further, the term "comprising" in claims 16 and 30 expands the drug moiety to include additional molecule or amino acids at either or both ends. Likewise, the term "comprising" in claim 24 expands the bifunctional molecule to include additional elements. There is inadequate written description about the undisclosed element to be added, let alone which intracellular proteins that the drug and targeting moiety of the bifunctional molecule bind for the claimed method.

Given the lack of a written description of *any* additional representative species of bifunctional molecule of less than about 5000 Daltons, any bifunctional comprising any drug or active derivative thereof and any targeting moiety that binds to any intracellular proteins, the claimed method is not adequately described. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 10/2/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the FK506, rapamycin, cyclosporin A and the like... on page 21 lines 3 to 5 of the specification are representative ligands capable of serving as the z moiety (targeting moiety) and not the drug moiety. (2) Each component of the bifunctional molecule, e.g., drug moieties (page 6 to 16), targeting moiety (page 16 to21) and linking moiety (pages 22 to 23) as well as how to make these targeted bifunctional molecules (page 24 to 28) are fully described in the specification.

However, the specific biodistribution modulating protein to which the targeting moiety binds may vary greatly depending on the desired biodistribution of the bifunctional molecule and drug moiety component thereof (page 18).

The specification on page 6 defines that the drug moiety X may be any molecule as well as binding portion or fragment thereof that is capable of modulating a biological process in a living host either by itself or in the context of the biodistribution modulating protein /bifunctional molecule binary complex. The drug moiety of the bifunctional molecule may be the whole compound or a derivative thereof. e.g. its binding fragment or portion thereof that retains its affinity and activity for the target of interest. 'I'he drug moiety is capable of interacting with a target ... where such targets may be proteins, phospholipids, nucleic acids and the like where proteins are of- particular interest. Specific protein targets of interest include- without limitation enzymes, e.g. kinases- phosphatases- reductases, Cyclooxygenases proteases and the like. The specification on page 21 discloses that ligands capable of serving as the Z moiety (targeting moiety) of the

bi functional include ligands the intracellular proteins. Such as: peptidyl-prolyl isomerase ligands- e.g. 17 14.506- rapamycin, cyclosporin A and the like.

However, given the infinite number of undisclosed drug moiety, targeting moiety in the biofunctional molecule, the claimed method of using said targeting molecule is not adequately described.

6. Claims 16-18, 22-23, 30-34 and 36 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

The "bifunctional molecule of less than about 5000 Daltons" in Claims 16 and 30 represents a departure from the specification and the claims as originally filed. The specification on page 6 discloses that the **drug moiety** of the bifunctional molecule has a molecule weight of at least about 50D, at least about 100 D, may be as high as 500D but will not exceed about 2000 D.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "mammalian host" in claim 32 has no antecedent basis in base claim 30. Claim 32 should depend from claim 31.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 16-18, 22-26, 30-34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pichon *et al* (of record, Mole Pharmacology 51(3): 431-38; 1997; PTO 892) in view of US Pat No. 5,830,462 (of record, Nov 1998, PTO 1449) and WO 95/10302 publication (of record, April 1995, PTO 1449).

Pichon *et al* teach a method for directing the biodistribution of a drug such as ODN-p-KDEL to an intracellular space upon such as the internal compartments containing the KDEL receptor, i.e. IC, the ER and the cis-Golgi apparatus (See page 434, Intracellular Localization, in particular). The reference bifunctional molecule consists of a drug such as ODN, which is a 25mer polynucleotide, and a targeting moiety such as KDEL that is linked through a linker such as a thio-carboxymethyl group which forms a thioester bond between said drug and said targeting moiety (See age 432, Materials and Methods, in particular). The reference bifunctional molecule exhibits enhanced efficacy by 5 fold upon administration to a mammalian host such as human hepatoma HepG2 cells (See page 433, Results, Biological Effect, in particular). The reference targeting moiety KDEL binds to the reference intracellular protein such as the KDEL receptor, golgi or ER. The reference bifunctional molecule is administered as a pharmaceutical preparation to inhibit expression of specific genes within cells and as a therapeutic agent for HIV in human (See page 431 and references 10-11 therein, in particular). The reference bifunctional molecule ODN-p-KDEL is a small molecule such as 15 peptides in length, which inherently is less than about 5000 Daltons (See page 432, oligonucleopeptide, in particular). The reference targeting moiety binds to an endogenous biodistribution modulating protein such as the KDEL receptor, which is also an intracellular protein located in the IC, the ER and the cis-Golgi apparatus (See page 434, Intracellular Localization, in particular).

The claimed invention in claim 16 differs from the teachings of the reference only that the method wherein the drug binds to a protein target.

The claimed invention in claim 30 differs from the teachings of the reference only that the method of administering a drug to a host in need of said drug comprising administering to said host an effective amount of a bifunctional molecule of less than about 5000 Daltons consisting of said drug moiety comprising said drug or a derivative thereof covalently linked either directly or through an optional linking group to a targeting moiety that binds to an intracellular biodistribution modulating protein, wherein said drug moiety binds to an intracellular protein

The claimed invention in claim 34 differs from the teachings of the reference only that the method of administering a drug to a host in need of said drug comprising administering to said host an effective amount of a bifunctional molecule of less than about 5000 Daltons consisting of said drug moiety comprising said drug or a derivative thereof covalently linked either directly or through an optional linking group to a targeting moiety that binds to an intracellular biodistribution modulating protein, wherein said drug moiety binds to an intracellular protein and said targeting moiety binds to an endogenous biodistribution modulating protein.

The '462 patent teaches various drug moiety such as FK506 that are small in size and binds to the endogenous biodistribution modulating protein such as peptidyl prolyl isomerase (FKBP12) or FKBP receptor which is an intracellular protein (See column 22, lines 62-64, in particular). The '462 patent further teaches other drug moiety such as cyclosporin A that binds to the cyclophilin receptor, the estrogen that binds with the estrogen receptor, the vitamin D that binds to the vitamin D receptor with high affinity (See column 22 lines 66-67 bridging column 23, line 1-27). The reference drug moiety such as FK506 is typically being at least about 150 D and few than about 5 kD, usually fewer than about 3 kD (See column 22, lines 62-64, in particular). The '462 patent teaches a targeting domain such as tyrosine kinase CD3 in the bifunctional molecule such as a tyrosine kinase CD3ζ fused to FKBP12 (See Fig 2, in particular) or the DNA binding domain (Gal4) fused to FK506 (See Abstract, Fig 2, column 17, line 14; column 21 line 23-26, in particular). The '462 patent further teaches that these moiety are linked together through a linking group (See column 24, lines 17-24, column 25, line 28-35, in particular). The '462 patent further teaches a pharmaceutical composition (See column 6, line 63-67 bridging column 7 lines 1-16, in particular). The '462 patent also teaches

chimeric protein can be target to a specific location by adding a signal sequence from the vesicle or golgi or ER which are intracellular space, for example (See claim 42 of '462, in particular). The '462 patent teaches the advantages of cyclosporin A2 and FK506 are they bind to their receptor with high affinity Kd $\leq 10^{-8}$ M (See column 23, line 11, in particular) and like FK1012s, it is neither immunosuppressive nor toxic (See column 27, lines 65-66, in particular).

The WO 95/10302 publication teaches that linking any drug to a targeting moiety could modulate the volume of distribution of the drug to ovoid non-specific undesired side-effects (See Abstract, Summary of the Invention, in particular).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to substitute the drug moiety in the bifunctional molecule such as the ODN in the ODN-p-KDEL as taught by Pichon *et al* for the FK506 in the FK-pYEEI bifunctional molecule as taught by the '462 patent for a method of directing the biodistribution of a drug that binds to a protein target to an intracellular space upon administration to a host as taught by Pichon *et al*, the '462 patent and the WO 95/10302 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. While the reference is silence with regard to compared the drug to a free drug control, it is within the purview of one ordinary skill in the art to establish the effectiveness of a drug by comparing to the control.

One having ordinary skill in the art at the time the invention was made would have been motivated with a reasonable expectation of success to substitute the drug moiety or the targeting moiety of any bifunctional molecule because the '462 patent teaches that targeting moiety such as FK506 binds to FKBP12 with high affinity Kd $\leq 10^{-8}$ M (See column 23, line 11, in particular); cyclosporin A binds to the cyclophilin receptor with high affinity (See column 27, lines 52, in particular) and like FK1012s, it is neither immunosuppressive nor toxic (See column 27, lines 65-66, in particular). Briesewitz *et al* teach that drugs such as cyclosporin and FK506 are presented by cyclophilin and human FK506 binding protein to inhibit the activity of a calcineurin. By themselves, FK506 and cyclosporin have no measurable affinity for calcineurin. The specificity and affinity of a ligand protein interaction could be modulated by chemically lining a ligand for an abundant cytosolic protein such as FKBP12 via chemical linkers of different lengths and biofunctional molecule is useful to modulate the potency and

specificity of biologically active compounds (See page 1953, column 2, first full paragraph, in particular). The WO 95/10302 publication teaches that linking any drug to a targeting moiety could modulate the volume of distribution of the drug to ovoid non-specific undesired side-effects (See Abstract, Summary of the Invention, in particular).

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
November 28, 2003

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